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ARTICLE

Model-based simulation to support the approval of isatuximab alone or with dexamethasone for the treatment of relapsed/refractory multiple myeloma in Japanese patients

Hoai-Thu Thai[1] | **Kimiko Koiwai**[2] | **Yoshihisa Shitara**[3] | **Hirotaka Kazama**[4] | **Jean-Baptiste Fau**[2] | **Dorothée Semiond**[5] | **Christine Veyrat-Follet**[1]

[1]Sanofi R&D, Data and Data Science, Translational Disease Modeling, Chilly-Mazarin, France

[2]Translational Medicine and Early Development, Sanofi, Chilly-Mazarin, France

[3]Translational Medicine and Early Development, Sanofi, Tokyo, Japan

[4]Specialty Care Oncology Medical, Sanofi, Tokyo, Japan

[5]Translational Medicine and Early Development, Sanofi, Cambridge, Massachusetts, USA

Correspondence
Hoai-Thu Thai, Translational Disease Modeling, Sanofi R&D, Data and Data Science, 1 Avenue Pierre Brossolette, Chilly Mazarin 91385, France.
Email: hoai-thu.thai@sanofi.com

Abstract

This study aimed to support dosing regimen selection for isatuximab as a single agent or in combination with dexamethasone for Japanese patients with relapsed/refractory multiple myeloma (RRMM). A joint model characterizing the dynamics of serum M-protein kinetics and its association with progression-free survival (PFS) was developed using data from 201 evaluable Japanese and non-Japanese patients with RRMM enrolled in two monotherapy phase I/II trials, where Japanese patients ($n = 31$) received isatuximab at 10 or 20 mg/kg once weekly (qw) for 4 weeks then every 2 weeks (q2w) in subsequent cycles (10 or 20 mg/kg qw–q2w). Among non-Japanese patients, 38 received isatuximab 20 mg/kg qw–q2w in combination with dexamethasone. Trial simulations were then performed to evaluate the effect of the isatuximab dosing regimens on both serum M-protein and PFS with and without dexamethasone. The model identified instantaneous changes in serum M-protein as the best on-treatment predictor for PFS. Trial simulations demonstrated that 20 mg/kg qw–q2w induced a greater decrease (30% vs. 22%) of serum M-protein at week 8 and prolonged median PFS by 2.4 weeks compared with 10 mg/kg qw–q2w. Although Japanese patients did not receive isatuximab plus dexamethasone in the phase I/II trial, simulations predicted that isatuximab 20 mg/kg qw–q2w plus dexamethasone would induce a greater decrease (67% vs. 43%) of serum M-protein and a prolonged median PFS by 7.2 weeks compared with isatuximab alone. Trial simulations support the approved isatuximab 20 mg/kg qw–q2w regimen when administered as a single agent and in combination with dexamethasone in Japanese patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Despite advances in treatment strategies, overall survival of patients with multiple myeloma (MM), especially those that are dual refractory to immunomodulatory agents (thalidomide or lenalidomide) and proteasome inhibitors (bortezomib or carfilzomib), remains poor. Isatuximab is approved in combination with pomalidomide/dexamethasone for these patients in many countries, and its optimal dosing can be selected using a nonlinear joint modeling framework.

WHAT QUESTION DID THIS STUDY ADDRESS?

Is there an association among serum M-protein kinetics, baseline covariates, and progression-free survival (PFS) in Japanese and non-Japanese patients with relapsed/refractory MM after treatment with isatuximab monotherapy as assessed by trial simulations? Is isatuximab 10 and 20 mg/kg qw–q2w ± dexamethasone beneficial in Japanese patients?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Isatuximab monotherapy at 20 mg/kg qw–q2w induced a significantly greater decrease of serum M-protein and prolonged median PFS compared with isatuximab 10 mg/kg qw–q2w. Short-duration dexamethasone combined with isatuximab would remain beneficial for a subgroup of patients with lower tumor burden and better prognostics.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Simulation model-based drug development approaches can be applied successfully to select and justify a dosing regimen, without conducting an additional trial.

INTRODUCTION

Despite advances and improvements in overall survival (OS), multiple myeloma (MM) remains an incurable disease, and most patients will relapse and require additional treatments.[1] The introduction of proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs) has improved clinical outcomes in patients with MM, and 5-year survival rates increased to 56% in 2011–2017.[2] However, survival declines with successive lines of therapy, and only 30% of patients with MM survive beyond 10 years.[3] Median OS is 13 months in patients with MM that is dual refractory to IMiDs and PIs.

Isatuximab (SARCLISA) is an IgG1-kappa monoclonal antibody that targets the CD38 transmembrane glycoprotein in MM cells via a specific epitope distinct from that targeted by daratumumab. Isatuximab induces tumor cytotoxicity via multiple mechanisms, and may also activate an antitumor immune response.[4–6] Isatuximab demonstrated single-agent activity and was generally well-tolerated in phase I/II studies in the United States and the European Union in heavily pretreated patients with relapsed/refractory MM (RRMM), including high-risk patients, and these responses were more durable at doses greater than or equal to 10 mg/kg.[7,8] Based on the results of the phase III ICARIA study, isatuximab 10 mg/kg weekly then every 2 weeks (qw–q2w) is approved in multiple countries, including Japan since June 2020, in combination with pomalidomide/dexamethasone (Pd).[9–11] Isatuximab is also approved in combination with carfilzomib/dexamethasone in the United States for patients who have received one to three prior lines, in the European Union for patients with greater than or equal to one prior therapy, and in Japan since November 2021.[9,10,12] A phase I/II study investigated the tolerability/safety and efficacy of isatuximab monotherapy in Japanese patients with heavily pretreated RRMM who had exhausted available options, including a PI and an IMiD.[13]

Joint modeling framework, including pharmacokinetics (PK) and dynamics of serum M-protein with dropout, has been used for isatuximab, first to integrate learnings from early clinical data during drug development and then confirming with data obtained after database lock from phase I/II monotherapy and phase I combination trials.[14] This provided support for phase II/III dosing regimen selection in patients with MM. This framework and modeling approach has been applied to the phase

TABLE 1 Study design.

Study	Study part	Isatuximab i.v. dosing	Number of treated patients	Number of patients used for modeling
NCT01084252 Phase II study (non-Japanese study)	Total		261	170
	Phase II stage 1	3 mg/kg q2w	23	13
		10 mg/kg q2w	25	14
		10 mg/kg q2w–q4w	24	17
		20 mg/kg qw–q2w	25	17
	Phase II stage 2	20 mg/kg qw–q2w alone	109	71
		20 mg/kg qw–q2w + dexamethasone[a]	55	38
NCT02812706 phase I/II study (Japanese study)	Total		36	31
	Phase I	10 mg/kg qw–q2w	3	3
		20 mg/kg qw–q2w	5	3
	Phase II	20 mg/kg qw–q2w	28	25

Abbreviations: i.v., intravenous; q2w, biweekly; q2w–q4w, biweekly for 8 weeks then every 4 weeks; qw–q2w, weekly for 4 weeks then biweekly.

[a]Dexamethasone at 40 mg/day [20 mg/day for patients ≥75 years] on days 1, 8, 15, and 22 of each cycle.

III ICARIA trial, allowing to well-characterize the relationship between serum M-protein kinetics and risk of progression-free survival (PFS) and identify the impact of baseline covariates (e.g., albumin, β2-microglobulin [B2MG], presence of plasmacytoma) in patients with RRMM receiving isatuximab plus Pd.[15] The present study evaluated isatuximab treatment as monotherapy or in combination with dexamethasone in both Japanese and non-Japanese patients to support submission in Japan using a similar framework. Therefore, the objectives of this study were to quantitatively evaluate the association among serum M-protein kinetics, baseline covariates, and PFS in Japanese and non-Japanese patients with RRMM after treatment with isatuximab monotherapy from two phase I/II trials and to assess the benefit of isatuximab 10 and 20 mg/kg qw–q2w ± dexamethasone in Japanese patients.

METHODS

Data and study design

Data were obtained from two phase I/II trials (NCT01084252 and NCT02812706) of single-agent isatuximab in non-Japanese and Japanese patients with RRMM, respectively.[7,8,13,16] The study protocols were approved by institutional review boards and independent ethics committees at the participating institutions. All patients provided written informed consent.

The study design and the number of patients used for modeling are summarized in Table 1. Additional study design details are presented in the Appendix S1.

Disease assessments

Disease assessments were performed every 4 weeks by an independent adjudication committee using the International Myeloma Working Group (IMWG) uniform response criteria, based on central laboratory M-protein assessments and radiology review.[17] Patients with greater than or equal to two serum M-protein values, including one baseline value, and for whom responses could be evaluated by serum M-protein were included in the analysis. Serum M-protein was assessed by serum protein and immunofixation electrophoresis. Per protocol, serum M-protein was measured at baseline, the end of each cycle (cycle = 4 weeks), and the end of the study. No lower limit of quantification (LLOQ) could be provided for serum M-protein measurement because M-protein and its structure are patient-specific. For this analysis, the LLOQ was considered as the actual lowest value for serum M-protein (i.e., 0.5 g/L).

Development of a joint model of serum M-protein and PFS

Serum M-protein longitudinal and PFS data were first modeled separately. To account for dose effect, treatment exposure over time was introduced in the longitudinal model using the concentrations predicted by the individual PK parameters obtained from the population PK model[18] for isatuximab and a kinetic-pharmacodynamic (K-PD) model[19] for dexamethasone (see details in Appendix S1).

First, we developed a longitudinal tumor growth inhibition (TGI) model of drug effect on tumor growth

dynamics based on the serum M-protein level. Claret's TGI model was used, which accounts for the dynamics of tumor growth, antitumor drug effect, and resistance to drug effect.[20] This model was successfully applied to describe serum M-protein data as a surrogate of tumor growth in patients with MM.[15,21–24] In this analysis, the mechanism-based TGI model was extended from the Thai et al.[15] model to describe the underlying disease progression and exposure-driven drug effect of isatuximab and dexamethasone on the time-course of serum M-protein by increasing tumor shrinkage rate. A linear effect model was used for dexamethasone, whereas a maximum effect (E_{max}) effect model was used for isatuximab. The structural model is described by the following differential equations:

$$\frac{dM}{dt} = \mathrm{KL} * M - \mathrm{KD} * \exp(-R * t) * \left(\frac{C_{\mathrm{iM}}}{\mathrm{EC50} + C_{\mathrm{iM}}} + k * C_{\mathrm{dM}}\right) * M$$

$$M(t = 0) = \mathrm{M0}$$

where M is serum M-protein at time t, $M0$ is the baseline serum M-protein, KL is the M-protein growth rate, KD is the M-protein shrinkage rate, R is the rate constant of resistance appearance to treatment, k is the coefficient for dexamethasone, EC50is the isatuximab concentration inducing half of its maximum effect, and C_{iM}, C_{dM} are the molar concentrations of Isa and dexamethasone at time t, respectively. The schematic representation of this model is found in Figure S1.

An exponential interindividual model implying a log-normal distribution was included on all parameters. The variance–covariance matrix was modeled using a diagonal matrix. The residual variability was modeled using a combined additive and proportional model.

The effects of 27 baseline covariates (Table S1) were evaluated on the TGI model. In case of missing data, the median value was input for continuous covariates; missing was considered as an additional category for categorical covariates. The parameter-covariate relationships were explored graphically using individual parameter estimates. The Conditional Sampling for Stepwise Approach based on Correlation tests (COSSAC) covariate selection algorithm was then used for automatic building of the covariate model.[25,26] The best covariate model was selected using the corrected version of Bayesian Information Criteria (BICc).[27] Only significant covariates with Wald-test $p < 0.05$ remained in the final model.

The PFS parametric proportional hazard model with log-logistic distribution for baseline hazard $h_0(t)$:

$$h_0(t) = \frac{\frac{s}{Te}\left(\frac{t}{Te}\right)^{s-1}}{1 + \left(\frac{t}{Te}\right)^{s}}$$

where Te is the scale parameter (characteristic time) and s is the shape parameter. Exponential and Weibull distribution were also tested.

The baseline covariates were then tested as potential prognostic factors using the classical stepwise covariate modeling method:

$$h_i(t) = h_0(t) \times \exp(\beta_w \times w_i)$$

where β_w is the vector of coefficients associated with the vector of baseline covariates w_i for individual i. The same criteria for covariate selection in the longitudinal M-protein model development was used.

Joint models were thereafter developed to fit simultaneously serum M-protein and PFS data using the previous longitudinal and PFS models. The link between serum M-protein kinetics and PFS was modeled using the following equation:

$$h_i(t) = h_0 \times \exp(\beta_w \times w_i + \beta_{\mathrm{link}} \times L(t))$$

where β_{link} denotes the coefficient associated with the link function $L(t)$

The following link functions $L(t)$ were evaluated:

- No link: β_{link}=0
- Current serum M-protein (predicted serum M-protein value over time): $M(t)$
- Current serum M-protein slope (instantaneous rate of change in serum M-protein): dM/dt

Significant covariates found in the longitudinal and PFS submodels were evaluated, only retaining significant covariates with the Wald test.

Parameter estimation of all models was performed using the Stochastic Approximation Expectation Maximization (SAEM) algorithm implemented in the software Monolix version 2020R1 (Lixoft). The data below the limit of quantification (LOQ) for serum M-protein were considered using the extended SAEM algorithm implemented in Monolix.

Model selection and evaluation

Model selection was based on BICc, retaining the model giving the lowest BICc. Model evaluation was performed by investigating residual- and simulation-based diagnostics, including the individual weighted residuals, visual predictive checks (VPCs) for the longitudinal part, and the Kaplan Meier VPC for the PFS part, respectively. Goodness-of-fit plots were assessed by visual inspection of individual fits or by comparing observations versus

individual predictions. Longitudinal VPC accounted for risk of progression using previously described methods.[28] The VPC for PFS considered patient's individual dosing history, follow-up duration, and censoring information in the data. The detailed steps for building the VPC of PFS are shown in the Appendix S1.

Simulation

Overall, 1000 trials of 201 patients were simulated using the theoretical dosing regimens of the protocol up to 20 months and patient characteristics in the observed data to evaluate the effects of isatuximab 10 or 20 mg/kg qw–q2w ± dexamethasone on serum M-protein dynamics and PFS for 20 months. The standard dexamethasone dosing regimen (40 mg qw for patients <75 years; 20 mg qw for patients ≥75 years) was the same as in phase I/II clinical trials. Short-duration dexamethasone administration (3 or 6 months) combined with isatuximab was evaluated by simulation and compared with the full duration of dexamethasone co-administration. Evaluation criteria were the change of serum M-protein at week 8 and median PFS.

RESULTS

Patient demography and clinical characteristics

A total of 201 among 297 patients with RRMM included in NCT01084252 phase II (non-Japanese; $n = 170$) and NCT02812706 (Japanese; $n = 31$) had exclusively serum M-protein or serum and urine M-protein with greater than or equal to two measurements of serum M-protein (1 post-treatment). Among these patients, 154 received isatuximab 20 mg qw–q2w, with 38 non-Japanese patients receiving isatuximab 20 mg qw–q2w combined with dexamethasone.

Table 2 presents baseline patient characteristics for each trial. Median age was 71 years (41.9% women) for the Japanese trial and 65 years (47.1% women) for the non-Japanese trial. Baseline median serum B2MG, serum albumin (ALB), and median estimated glomerular filtration rate were 3.4 mg/L, 36 g/L, and 86 mL/min/1.73 m^2, respectively, for the Japanese trial and 4.63 mg/L, 35 g/L, and 74 mL/min/1.73 m^2, respectively, for the non-Japanese trial. The percentage of patients with severe International Staging System (ISS) stage (stage III) was higher (37.6% vs. 12.9%) in the non-Japanese trial compared with the Japanese trial.

Safety profiles

Isatuximab was well-tolerated up to the highest tested dose of 20 mg/kg q2w ± a loading phase (4 weekly administrations) in both Japanese and non-Japanese patients. No clear exposure-response was evidenced between the PK exposure parameters (maximum plasma concentration [C_{max}], area under the curve [AUC], and trough plasma concentration [C_{trough}]) and the safety end points of interest (infusion reactions and hematologic adverse events), based on pooled analyses.

Best final joint model of serum M-protein kinetics and PFS

A total of 1774 serum M-protein observations in 201 evaluable patients were considered, with a median of 9 (range, 2–34) assessments/patient. The data below the LOQ accounted for 4%, with all from the Japanese study.

The longitudinal TGI model with an E_{max} effect of the isatuximab concentration on serum M-protein shrinkage best fitted the serum M-protein data with lowest value of BICc, which decreased 58 points compared with the model with a linear effect. The final longitudinal TGI model included seven covariates: effect of IgG MM type (IgG vs. non-IgG), baseline serum ALB, alkaline phosphatase (ALK), the number of prior lines of therapy, a Japanese study effect on the baseline serum M-protein levels, the refractory status to lenalidomide (yes/no) on KL (serum M-protein growth rate), and the observed serum M-protein levels at baseline on KD (M-protein shrinkage rate). A K-PD model of both isatuximab and dexamethasone was also tested for the TGI model, but its performance was worse than the model with isatuximab PK (increase of 34 points in BICc).

Regarding PFS, a log-logistic model best characterized the underlying baseline hazard distribution, with lowest BICc. Baseline covariates, such as ALK, B2MG, alanine aminotransferase, presence of plasmacytoma (yes/no), and dexamethasone co-administration (yes/no), were significant ($p < 0.005$).

The joint model to assess the best link between serum M-protein and PFS was developed using the final longitudinal and PFS models in the previous step. The serum M-protein slope outperformed other models in terms of BICc with a decrease of 78 points versus the model without association between serum M-protein and PFS, and a decrease of 9 points versus the models based on the current serum M-protein value. The comparison of statistical criteria between different link models is presented in Table S2. In the best final joint model, the longitudinal

TABLE 2 Baseline demographics and patient characteristics in serum M-protein population.

	All ($n = 201$)	Non-Japanese phase II trial ($n = 170$)	Japanese trial ($n = 31$)
Age, years (range)	66 (37–84)	65 (37–84)	71 (56–82)
Sex, *n* (%)			
Female	93 (46.3)	80 (47.1)	13 (41.9)
Male	108 (53.7)	90 (52.9)	18 (58.1)
Weight (kg), median (range)	70.0 (37.6–153)	71.9 (39.9–153)	55.3 (37.6–75.0)
Race, *n* (%)			
White	142 (70.6)	142 (83.5)	0
Black	12 (6.0)	12 (7.1)	0
Asian	32 (15.9)	1 (0.6)	31 (100)
Others	15 (7.5)	15 (8.8)	0
eGFR (mL/min/1.73m^2), median (range)	76.2 (18.7–217)	74.0 (18.7–186)	86.0 (39.3–217)
ISS, *n* (%)			
I	57 (28.4)	45 (26.5)	12 (38.7)
II	76 (37.8)	61 (35.9)	15 (48.4)
III	68 (33.8)	64 (37.6)	4 (12.9)
Serum β2-microglobulin (mg/L), median (range)	4.53 (1.32–19.5)	4.63 (1.32–19.5)	3.40 (1.90–12.7)
Serum albumin (g/L), median	35 (18–48)	35 (22–48)	36 (18–42)
Serum M-protein at baseline (g/L), median (range)	28.1 (6–84)	28.1 (6.1–84)	24 (6–73)
Ig MM type, *n* (%)			
IgG	139 (69.2)	114 (67.1)	25 (80.6)
Non-IgG	31 (15.4)	56 (32.9)	6 (19.4)
Plasmacytomas, *n* (%)			
No	170 (84.6)	145 (85.3)	25 (80.6)
Yes	31 (15.4)	25 (14.7)	6 (19.4)
Cytogenetic risk at study entry, *n* (%)			
Standard	120 (59.7)	102 (60.0)	18 (58.1)
High	53 (26.4)	42 (24.7)	11 (35.5)
Missing	28 (13.9)	26 (15.3)	2 (6.45)

Abbreviations: eGFR, estimated glomerular filtration rate; ISS, International Staging System; MM, multiple myeloma.

model includes the same seven baseline covariates; however, only three baseline covariates (the presence of plasmacytomas, dexamethasone co-administration, and B2MG) remain on the PFS part. Parameter estimates obtained with the serum M-protein slope joint model with covariates are summarized in Table 3 and the comparison with the base model for the longitudinal part is presented in Table S3. Parameters were reasonably well-estimated with low relative standard error for both fixed effects and variance components. The isatuximab concentration inducing EC_{50} on stimulating M-protein shrinkage rate was estimated to be 1.13 mol/L (equivalent to 170 mg/L). The coefficient of the impact of serum M-protein slope over time on PFS was estimated to be 6.65. The interindividual variability (IIV) on M0 decreased from 54.1% to 39.8% when including the covariates, indicating that the baseline covariates on M0 explain 14.3% IIV on M0. However, a very small decrease of the IIV on KL and KD was obtained with the covariate model. Of note, the estimated coefficient of B2MG effect on PFS is extremely low and negative, which may be related to some confounding factors. The serum M-protein kinetic patterns were well-captured by the model and predicted PFS probability is consistent with occurrent time of progression or censored event (see Figure S2 for examples of individual fits). Figure 1 shows VPC plots for both longitudinal and PFS models by simulation of 1000 clinical trials under the final joint model. The model described reasonably

TABLE 3 Parameter estimates values (RSE %) of the best joint final model.

Fixed parameter	Estimate	RSE (%)	Shrinkage (%)	*p* value
Longitudinal submodel				
M0 (g/L)	27	3.78		
β1~non_IgG	−0.255	24.5		4.49 E-05
β2~ALBN	−1.83	9.02		<2.2 e-16
β3~ALKN	−0.233	29.7		0.000759
β4~LINE	0.21	32.2		0.00189
β5~Japanese study	−0.216	37.5		0.00766
KL (day^{-1})	0.00531	9.05		
β6~REF_Len = *N*	−0.514	33.1		0.00255
KD ($L.mol^{-1}.day^{-1}$)	0.0396	9.17		
β7~MPROT	−0.56	25.5		9.07 E-05
R (day^{-1})	0.0192	11.1		
EC50 (mol/L)	1.13	15.4		
k	5.47	2.99		
Time-to-event submodel				
Te	272	15.5		
s	1.56	5.7		
β8~Dex = Y	−0.363	26.1		0.00013
β9~PCYTOMA = Y	0.799	43.5		0.0214
β10~B2MG	−1.76 E-07	17.5		1.08 E-08
β11~SlopeM	6.65	19.7		3.85 E-07
Interindividual variability (%)				
ω _M0	39.8	5.14	0.92	
ω_KL	94.7	6.37	17.5	
ω _KD	87	8.59	33.8	
ω _R	113	8.5	23.5	
ω _EC50	123	14.1	59.5	
Residuals				
σ additive (g/L)	0.477	5.94		
σ proportional (%)	7.21	4.59		
ε shrinkage			20.1	

Abbreviations: ALBN, baseline serum albumin normalized to the upper limit value; ALKN, alkaline phosphatase normalized to the upper limit value; b, coefficient of covariate effect; B2MG, beta-microglobulin; Dex, Y, co-administration with dexamethasone; LINE, number of lines of treatment; MPROT, observed baseline M-protein; PCYTOMA, Y, presence of plasmacytomas; REF_Len, N, no refractory to lenalidomide; RSE, relative standard error.

well the observed serum M-protein and PFS data in each trial with observed median generally included in the 90% prediction interval. An overprediction for risk of progression was observed for the Japanese trial after 30 weeks due to the small sample size and few patients remaining. Figure S3 shows the VPC plots stratified by dexamethasone co-administration. The joint model predicted reasonably well the median PFS for patients treated with isatuximab alone (19.1 weeks [P5–P95: 15.7–23.5] vs. 20.3 weeks). However, for isatuximab plus dexamethasone, the model underpredicted median PFS (28.6 vs. 53 weeks), possibly due to the limited sample size, but predicted well the hazard ratio (HR) of the effect of dexamethasone in the non-Japanese phase II stage II study (Figure S4). Other goodness-of-fit plots are presented in Figure S5.

Assessment of covariate effects

Simulations were performed to quantify the impact of each covariate using the population parameters and were

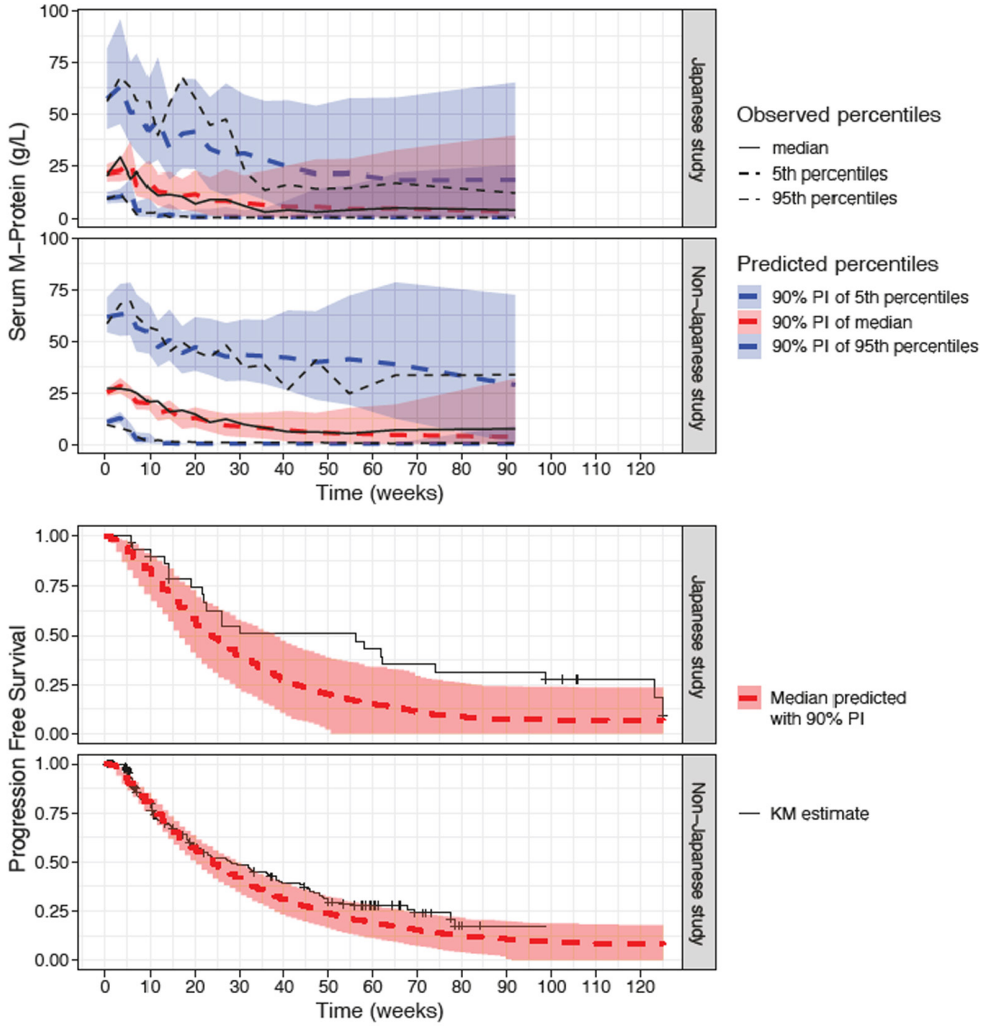

FIGURE 1 Visual predictive checks for serum M-protein and PFS of the final joint model stratified by study. Shaded area and the dotted lines represent the 90% prediction interval and the predicted median of 5th, 50th, and 95th percentiles of simulated M-protein or PFS data ($n = 1000$). The solid lines represent the 5th, 50th, and 95th percentiles of observed M-protein data or observed Kaplan–Meier estimate. CI, confidence interval; I, isatuximab; KM, Kaplan Meier; M-P, M-protein; PI, prediction interval; PFS, progression-free survival.

visualized in a typical patient (Figure S6). Patients with lower serum M-protein at baseline and treated with dexamethasone tend to have longer PFS whereas patients with plasmacytomas have shorter PFS. Patients with low ALB or refractory to lenalidomide tend to have faster serum M-protein regrowth and shorter PFS. There is a limited impact of the number of prior lines, ALKN, serum B2MG, and immunoglobulin G (IgG) MM type on PFS. When compared to non-Japanese patients, Japanese patients tend to have lower baseline serum M-protein, lower serum protein profile over time, and longer PFS.

Model-based simulations

The simulated results of dose effect on serum M-protein and PFS between isatuximab 10 mg/kg and 20 mg/kg qw–q2w are presented in Figure 2. Simulations demonstrated that isatuximab 20 mg/kg qw–q2w induced a greater decrease of tumor burden (serum M-protein) at week 8 (median decrease of 30% vs. 22%, respectively) and would prolong median PFS by 2.4 weeks versus 10 mg/kg qw–q2w. The simulated median HR for 20 mg/kg versus 10 mg/kg was 0.88 (p5-p95: 0.87–0.9), in favor of 20 mg/kg.

Comparisons of isatuximab qw–q2w ± dexamethasone in all patients and in Japanese patients were also conducted by simulation at isatuximab 20 mg/kg qw–q2w (Figure 3). In both Japanese and non-Japanese patients, isatuximab plus dexamethasone was predicted to induce a greater decrease of serum M-protein at week 8 (54% vs. 30%, median decrease from baseline) and prolonged median PFS by 6.3 weeks over isatuximab alone. Similar trends were observed for isatuximab plus dexamethasone in Japanese patients, with a greater decrease in serum

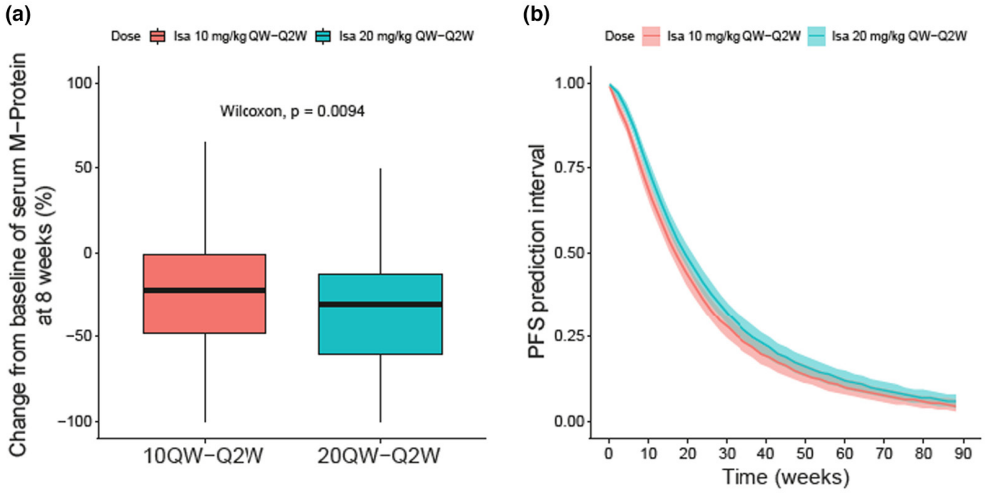

FIGURE 2 Simulated change of serum M-protein at week 8 (a) and simulated PFS profiles with prediction interval (b) for Japanese patients receiving isatuximab at 10 mg or 20 mg/kg qw-q2w.

M-protein at week 8 (67% vs. 43%, median decrease) and prolonged median PFS by 7.2 weeks versus isatuximab alone.

We also investigated by simulation the outcome when dexamethasone is used for a short duration of 3 or 6 months plus isatuximab 20 mg/kg qw–q2w. Table 4 summarizes the predicted median PFS of four scenarios. In all patients, median PFS was predicted to be prolonged by 1.5 and 2.0 weeks, respectively, and the median HR was predicted to be 0.91 and 0.89, respectively, for isatuximab plus dexamethasone for 3 or 6 months versus isatuximab alone. Similar findings were predicted in Japanese patients. However, stopping dexamethasone coadministration at 3 or 6 months would shorten median PFS by 5.6 weeks in patients at risk at 3 or 6 months (i.e., patients who would not progress during the first 3 or 6 months of treatment). When considering time to progression (TTP) criteria (increase in serum M-protein >25% with an absolute increase >5 g/L), 112 of 160 (70%) and 61 of 118 (51.7%) patients who stopped dexamethasone at 3 or 6 months had serum M-protein regrow faster and would progress earlier than patients who continue dexamethasone. Evaluation of baseline characteristics and M-protein response at 6 months was performed to compare patients with no risk of earlier progression with those who would progress earlier when stopping dexamethasone co-administration at 6 months (Figure S7). Patients with no risk of earlier progression had less baseline disease burden (i.e., lower serum M-protein and fewer bone marrow plasma cells), and better prognostic characteristics at baseline (i.e., higher ALB and lower B2MG with less frequent ISS II–III versus ISS stage I disease, 59.6% vs. 75.4%). At 6 months, they would have significantly lower M-protein (median, 1.46 vs. 4.74 g/L, $p < 0.0001$) and more patients would have reached their maximum response, with a serum M-protein slope closer to 0 (i.e., M-protein level reached a plateau, median slope of −0.03 vs. −0.07, $p = 0.0003$). More patients (54.4% vs. 31.1%) were predicted to have very good partial response or better. Similar trends were observed in Japanese patients despite the small sample size.

DISCUSSION

Joint models are increasingly used in clinical trials because they provide more efficient estimates and reduced bias of treatment effects on time to event and the longitudinal marker. In this analysis, we developed a joint model of serum M-protein (surrogate of tumor burden) and PFS to explore the best link between this biomarker and the clinical end point. The model was built using 201 evaluable patients from two monotherapy studies with 170 non-Japanese and 31 Japanese patients with RRMM.

The longitudinal data of serum M-protein was analyzed using Claret's TGI model, which has been used previously for MM.[15,21,22,24] Because isatuximab PK and dexamethasone dosing history were considered to predict treatment exposure, which increases serum M-protein shrinkage rate, this model allowed simulation of serum M-protein response to compare different dosing regimens for isatuximab (10 and 20 mg/kg qw–q2w) ± dexamethasone.

Several links between serum M-protein dynamics and PFS were evaluated in the joint model and the instantaneous change of serum M-protein (slope) was found to be the best link, consistent with the IMWG criteria in which the decrease in serum M-protein in response to treatment is the main component directly impacting PFS. This finding is similar to previous findings using data from the

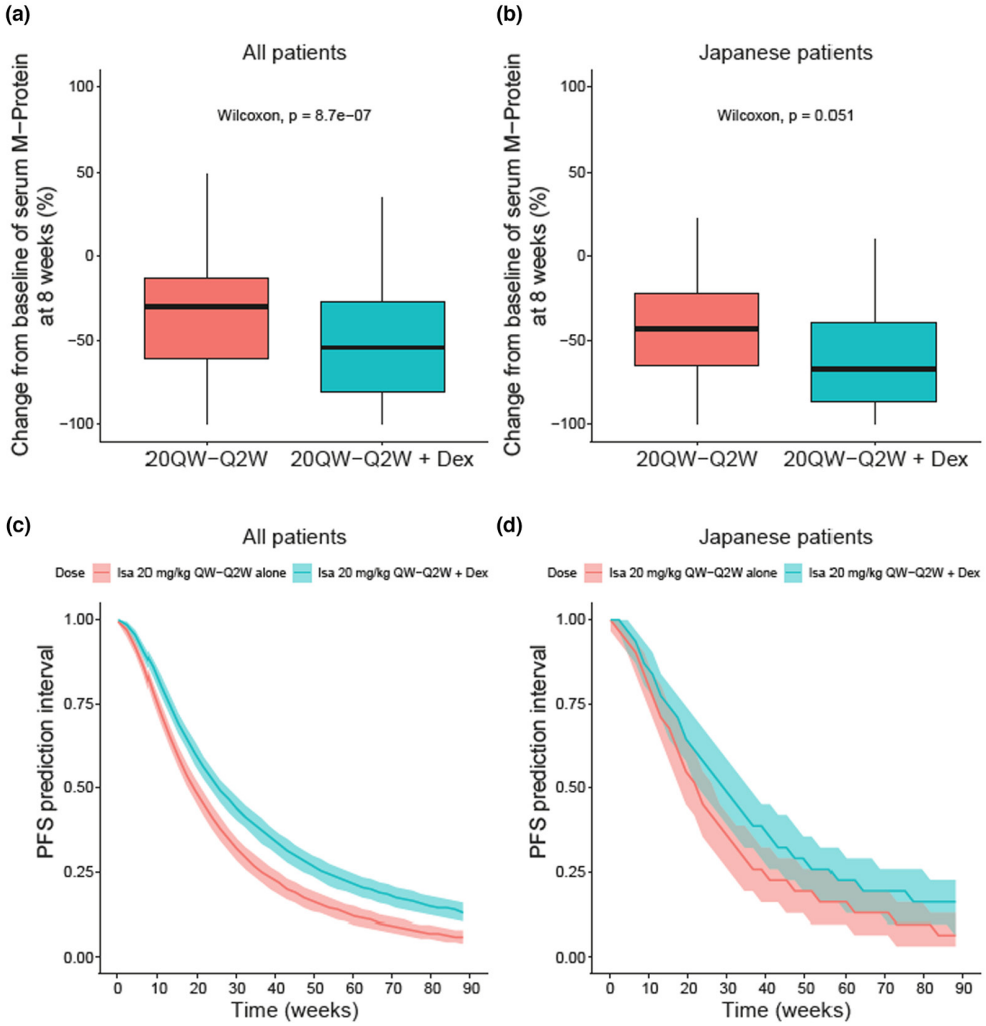

FIGURE 3 Simulated change of serum M-protein at week 8 in all patients (a) in Japanese patients (b) and simulated PFS profiles with prediction interval in all patients (c) in Japanese patients (d) receiving isatuximab at 20 mg/kg qw–q2w with or without dexamethasone.

TABLE 4 Simulated median PFS with prediction interval.

	Dosing regimens	Median PFS (weeks) (P5–P95)	Delta (weeks) (P5–P95)	HR (P5–P95)
All patients ($N = 201$)	Isa 20 mg/kg qw–q2w alone	19.3 (17.5; 21.3)		
	Isa 20 mg/kg qw–q2w + Dex	25.6 (22.9; 28.6)	6.3 (5; 7.9)	0.71 [0.68; 0.74]
	Isa 20 mg/kg qw–q2w + Dex 0_3M	20.9 (18.8; 23.1)	1.54 (0.52; 2.63)	0.91 [0.9;0.93]
	Isa 20 mg/kg qw–q2w + Dex0_6M	21.3 (19.1; 23.7)	2 (0.9; 3.1)	0.89 [0.88;0.91]
Japanese patients ($N = 31$)	Isa 20 mg/kg qw–q2w alone	22.2 (17.4; 27.4)		
	Isa 20 mg/kg qw–q2w + Dex	29.3 (22.1; 38.2)	7.2 (3.9; 11.7)	0.70 [0.62;0.77]
	Isa 20 mg/kg qw–q2w + Dex0_3M	23.6 (17.8; 30.5)	1.5 (−1.5; 4.5)	0.93 [0.87;0.99]
	Isa 20 mg/kg qw–q2w + Dex0_6M	24.2 (18.0; 31.1)	1.9 (−1.2; 5.5)	0.91 [0.85;0.98]

Note: Delta: difference of median PFS compared to Isa 20 mg/kg qw–q2w alone, P5–P95: 5th and 95th percentiles.

Abbreviations: Dex, dexamethasone; HR, hazard ratio with respect to Isa 20 mg/kg qw–q2w alone; Isa, isatuximab; PFS, progression-free survival.

ICARIA-MM phase III trial.[15] However, the coefficient effect of slope was less important, at half the estimated value in the ICARIA joint model (6.65 vs. 11.9).

With the joint model, we also studied the impact of baseline covariates on both serum M-protein kinetics and risk of PFS, such as patient demographics, baseline

laboratory values, and disease-related characteristics. The most important baseline covariates were serum ALB, serum M-protein, presence of plasmacytoma, dexamethasone co-administration, and refractory status to lenalidomide; other covariates (e.g., ALKN, B2MG, Ig MM type, and number of lines) had very limited impact. Patients with lower serum M-protein at baseline tended to have slower M-protein regrowth and longer PFS versus others. A similar trend was observed for patients treated with dexamethasone, as they had a better response profile compared with patients who did not receive dexamethasone. Patients with presence of plasmacytomas tend to have shorter PFS. Patients having low ALB or patients with refractory to lenalidomide tended to have faster serum-M-protein regrowth and shorter PFS. In our analysis, Japanese patients had lower serum M-protein concentration time profile and longer PFS versus non-Japanese patients. This is a confounding factor because Japanese patients involved in the Japanese clinical trial presented with a less advanced disease state, a lower tumor burden at baseline (lower bone marrow plasma cell involvement, lower serum B2M, fewer patients with stage III ISS, and a higher proportion of patients with Eastern Cooperative Oncology Group [ECOG] = 0). The population PK analysis also showed a higher exposure to isatuximab in Japanese patients with lower linear clearance, possibly due to their better prognostic characteristics at baseline.

Simulations of dose effect on both serum M-protein and PFS were conducted using the final joint model and demonstrated that isatuximab monotherapy (20 mg/kg qw–q2w) induced a greater decrease of serum M-protein (30% vs. 22% at week 8) and a median PFS prolonged by 2.4 weeks compared with isatuximab (10 mg/kg qw–q2w). A previous exposure-response analysis on isatuximab monotherapy also demonstrated that log C_{trough} at 4 weeks was a significant predictor of response rate and supported the choice of 20 mg/kg qw–q2w for monotherapy.[14] For the combination therapy, the relationship between exposure-response is less important. Koiwai et al.[24] demonstrated that the difference between 10 and 20 mg/kg qw–q2w on serum M-protein reduction was minimized when combining isatuximab with lenalidomide/dexamethasone or pomalidomide/dexamethasone, suggesting 10 mg/kg qw–q2w was a good choice for combination therapy. This finding is in agreement with the exposure-response analysis performed by Rachedi et al.[29] The different doses of isatuximab between monotherapy and combination therapy (20 vs. 10 mg/kg) were chosen based on the benefit–risk evaluation. Furthermore, it can be noted that the lower dose for combination therapy, while maintaining efficacy, reduces the infusion time by 2 h and makes the administration more convenient for patients.

In the phase II monotherapy non-Japanese trial, isatuximab 20 mg/kg qw–q2w plus dexamethasone was also evaluated in a subgroup of patients in stage II, and this combination showed a higher overall response rate versus isatuximab alone (43.6% vs. 23.6%). The addition of dexamethasone to daratumumab, another anti-CD38 monoclonal antibody, was also found to be safe and effective for heavily pretreated patients with MM who had previously failed lenalidomide, pomalidomide, and bortezomib, in an open-label phase II study.[30] Dexamethasone was assumed to have an additive effect on daratumumab and helped control early progression. However, a head-to head comparison between daratumumab alone and with dexamethasone is not available. In our analysis, to assess the benefit of isatuximab/dexamethasone, particularly in Japanese patients, we performed an additional simulation study to compare isatuximab 20 mg/kg qw–q2w ± co-administration with dexamethasone in this patient population using baseline characteristics and PK and serum M-protein dynamics. Like the observations in non-Japanese patients, isatuximab 20 mg/kg qw-q2w plus dexamethasone was predicted to induce a greater decrease of serum M-protein (67% vs. 43% for median decrease at week 8) and a prolonged median PFS by 7.2 weeks in Japanese patients versus isatuximab 20 mg/kg qw–q2w alone. Due to overprediction of risk of progression for isatuximab plus dexamethasone, the clinical benefit of using dexamethasone in combination with isatuximab versus isatuximab alone should be greater than these predictions. This in silico trial provided important insights into the benefit of co-administration of isatuximab/dexamethasone in Japanese patients with RRMM and supported the approval of isatuximab plus dexamethasone in Japan without an additional clinical trial.

Dexamethasone is commonly used in combination with other drugs in MM; however, sustainable use of dexamethasone is often not desirable in heavily treated patients due to the increased risk of complications, including infection coming from neutropenia and lymphopenia.[31,32] Short-term use of dexamethasone makes infection control easier and can be an option for the benefit–risk balance. The drug-disease modeling platform was therefore further applied to predict the impact of using hypothetical dosing regimens when dexamethasone can be used only for a short duration of 3 or 6 months in combination with isatuximab 20 mg/kg qw–q2w in patients with RRMM. In patients still on treatment, simulations of a hypothetical discontinuation of dexamethasone co-administration at 6 months predicted progression to occur 1.9 weeks earlier versus the sustained use of dexamethasone, with 51.7% of patients having their serum M-protein regrow faster. Patients with no risk of earlier progression tended to have lower tumor burden and better prognostic characteristics

at baseline, with a stable, very good partial response or better at 6 months, which was similar to our previous monthly dosing regimen evaluation using ICARIA-MM trial data.[15] Short-duration dexamethasone plus isatuximab remains beneficial for a subgroup of patients with lower tumor burden and better prognostics. These analyses confirmed the choice of the selected isatuximab 20 mg/kg qw–q2w dosing regimen for monotherapy and recommended isatuximab 20 mg/kg qw–q2w plus dexamethasone as an effective option for Japanese patients with MM relapsed/refractory to treatment with both PI and IMiD agents. Based on these findings, Japan approved isatuximab ± dexamethasone in November 2021.

AUTHOR CONTRIBUTIONS

H.T.T., K.K., Y.S., H.K., J.B.F., D.S., and C.V.F. wrote the manuscript. H.T.T., K.K., Y.S., H.K., J.B.F., D.S., and C.V.F. designed the research. H.T.T., K.K., J.B.F., and C.V.F. performed the research. H.T.T., K.K., Y.S., H.K., J.B.F., D.S., and C.V.F. analyzed the data.

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H.-T.T., K.K., Y.S., H.K., J.-B.F., D.S., and C.V.F. are employees of Sanofi and may hold shares and/or stock options in the company.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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